Practical Anticonvulsant Pharmacokinetics*

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Pharmacokinetic Considerations. Pharmacokinetics is that area of pharmacology concerned with the absorption, distribution, metabolism, and elimination of drugs. The processes by which absorption, distribution, and elimination take place are referred to as unit processes. These occur independently and concurrently, and involve such activities as absorption into the blood, elimination from the blood, distribution between the blood and tissue, inactivation in tissues, and finally, elimination from the blood. Drug handling by the body can be characterized by the rate for each step or, more often, the rate of all processes. Classification of observed kinetics for these rate processes includes first-order, zero-order, and capacity-limited kinetics. In the description of these processes, we will use total body elimination as the model, as this is the way most data are handled clinically (1).

The rate of first-order or exponential drug elimination is proportionate solely to the amount of drug present. The half-life is constant regardless of the quantity present. Thus, if the dosage is doubled, the half-life will remain the same.

Zero-order kinetics is the term used to describe processes where rates are constant per unit time; the time required to rid the body of one-half the drug is prolonged by increasing the body load. It is implied that the rate process is limited, and the rate of elimination is fixed.

Capacity-limited kinetics describe a situation of a rate process being variable and between the limiting situations of first and zero-order. As the number of drug molecules approximates the number of metabolic sites, for example, special mathematical processes must be employed to describe the responses. As drug levels rise, the rate approaches the zero-order rate (constant amount eliminated/time) and as levels fall, first-order rates are approximated.

If we consider the situation of drug overdose or intoxication, it may help to clarify these different kinetic patterns. If zero kinetics are operative as in alcohol, the patient will rid himself of the same number of milligrams each hour regardless of serum level. At high levels in the body, this constant amount is a very small percent of body load and the rate of decline of serum concentration is slow indeed. If first-order kinetics attain, as with phenobarbital, the total body load in the intoxicated patient will decline to one-half in the same time as the amount in the patient with a therapeutic amount. The situation of satura-

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tion kinetics is an intermediate between the two. An understanding of these principles is important mainly for preventing intoxication, for efficient alteration of dosage, and for understanding individual variations.

While the determination of rate constants is important, other parameters are of concern. Absorption parameters include both the rate of absorption and the bioavailability or percentage of the drug absorbed which reaches the active sites in the body. Distribution parameters include not only the rate of distribution but also the volume of distribution or extent to which the drug is found outside the blood; this is affected by protein binding. Protein binding may be affected by disease states and other drugs.

The pharmacologic effect on the desired organ or organ system will be dependent upon the amount of time in the body, the time exposed to the target organ, and the specific properties of the drug used. The occurrence of side effects is dependent upon similar considerations.

There are many patient variables such as individual physiology, pathology, and genetic characteristics, as well as developmental and environmental factors which effect drug response. A drug serum assay (drug level determination) is but a small part of the data necessary to make an intelligent judgment with regard to maximizing the desired effect in therapy. Serum assay determines only the quantity in the serum and basic assumptions must be made in regard to the organ or organ system where the drug is active. Many factors affect the relationship between serum concentration and drug effect. An understanding of pharmacokinetic principles will result in less trial-and-error pharmacotherapy and more frequent consideration of important variables. For example, if the physician, as his goal in treating the seizure patient, has established that a patient should have no subsequent seizures, then he will, with a basic understanding, be able to prevent some of the seizures which occur during the start-up and dosage-adjustment phases of drug therapy; he may also avoid intoxication.

Clinical Considerations. The availability of drug assays and pharmacokinetic data has already provided some useful information for the clinician (2). This has increased our knowledge in four areas: the initiation of therapy, dosage regimens, routes of administration, and adjustment of dosage for the four basic anticonvulsants—phenobarbital, diphenylhydantoin (Dilantin®), primidone (Mysoline®), and ethosuximide (Zarontin®). These are the most commonly used agents, and there are, consequently, more pharmacokinetic data regarding them.

Initiation of Therapy. With respect to the initiation of dosage, there is a rule of thumb that can be helpful: If a maintenance dosage regimen is used to initiate therapy, four times the half-life of the agent will be required to achieve 90% of the ultimate serum plateau. Since such a long time is required to reach this plateau with some drugs, such as diphenylhydantoin, loading has been used, particularly to achieve rapid therapeutic levels. Phenobarbital and primidone, however, produce significant drowsiness, so they are usually not "loaded." With ethosuximide, employed in the treatment of absence seizures, loading doses are usually not used because of the mild nature of the seizure being treated. Agents with long half-lives, however, are, potentially, those with which the initial dose should be larger than the maintenance dose.

The usual starting dose for phenobarbital is 5 mg/kg/day in the child and about 1 mg/kg/day in the adult. The half-life is 18–70 hours in a child (3) and 55–120 hours in the adult (4). In general, the younger the individual, the shorter the half-life.

The starting dose for diphenylhydantoin is 5–8 mg/kg/day for the child and 4–6 mg/kg/day for the adult. Once the therapeutic level is achieved, the apparent half-life is 8–12 hours. Loading of diphenylhydantoin can be accomplished by giving three times the maintenance dose in three divided doses, three hours apart on the first day (5); the second day, the usual maintenance dose is given. Therapeutic levels are reached in 12 hours, and peak serum levels are usually achieved on the third day. Diphenylhydantoin may also be loaded intravenously with accompanying electrocardiographic monitoring, but not more than 50 mg/minute should be given (6).

The initial dose of primidone administered is less than the maintenance level because of the initial potent hypnotic side effects. Usually, a maintenance dose of 20 mg/kg/day is sought. Switching a patient from phenobarbital to full maintenance primidone usually can be accomplished without producing sedative side effects. The half-life of primidone is short—3–12 hours (7).

The starting dose of ethosuximide is 20 mg/kg/day. The half-life is a mean of 66 hours in an adult and 30 hours in a child.

Dosage Regimens. Because phenobarbital and ethosuximide have long half-lives, once-daily ad-

ministration can be employed, and because of diphenylhydantoin's slow absorption, it also can be given once daily. Primidone, having a relatively short half-life, generally, should be given three times a day, although some patients are well treated with twice-daily dosage. Ethosuximide may have a gastric irritant effect, so some clinicians employ it in a twice-daily regimen.

Routes of Administration. Ethosuximide and primidone can be given only orally. Phenobarbitol can be given orally, intramuscularly or intravenously. While diphenylhydantoin can be given orally or intravenously, intramuscular administration usually fails to release sufficient diphenylhydantoin to the blood, when given as the usual maintenance dose. Doubling the maintenance dose when giving it intramuscularly is satisfactory, particularly when using this route for short-term replacement of oral therapy, as in surgery (8).

Adjustment of Dose. In adjusting the level of medication, one should remember that phenobarbital and ethosuximide are eliminated by first-order kinetics and diphenylhydantoin, by capacity-limited kinetics (9). Consequently, doubling the dose of phenobarbital will double the blood level, as trebling the dose will triple the blood level. When levels of diphenylhydantoin are low, a similar relationship exists. At higher levels, in practice, apparently, above 10 μg/ml, the effect of capacity-limited kinetics is that apparently relatively small dosage increments result in greater serum level increases than is expected or desired. Half increments are probably in order here. The therapeutic ranges given for phenobarbital levels are 10–50 μg/ml, for primidone are 5–20 μg/ml, and for ethosuximide are 40–80 μg/ml. The therapeutic range for diphenylhydantoin is 6–20 μg/ml. Recent work indicates that low serum levels are effective in controlling seizures particularly in children.

Compliance. While our knowledge of pharmacokinetics has increased, one larger problem exists in the area of compliance. Compliance is poor when administration of the drug is too frequent, when multiple drugs are used on a different schedule, and when the dosage form is unacceptable.

Three of the anticonvulsants mentioned can be given as infrequently as once a day. This eliminates the necessity for children to take these agents in school. When multiple agents are given, it is relatively easy to give all medications at one time.

Phenobarbital is available as an elixir, diphenylhydantoin and primidone, as suspensions. Where it is possible, the tablet form assures a more reliable dosage intake. In the young child, all can be crushed and given with jelly or other vehicles. Diphenylhydantoin comes as a chewable tablet, and while it may produce more gingival hypertrophy than the capsule, we continue to use it extensively. Ethosuximide constitutes a rather special problem being a liquid within a rather large gelatin capsule. The capsule can be pricked by a pin and the liquid mixed with juice or another vehicle by the pharmacist or mother. One ingenious mother related that the capsule can be frozen, then cut in half and given with ice cream.

Memory crutches are useful. The most inexpensive is the traditional egg carton. Dial-a-packs are also available and can be loaded by the patient with his drug or drugs.

A new era is here. Practical pharmacokinetics, skillfully utilized by the clinician, should aid immeasurably in producing seizure-free patients and in reaching the goal quickly with fewer side effects.

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